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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,084	12/05/2005	Christine Vauthier	BJS-5006-5	9469

23117 7590 05/24/2010
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EXAMINER	
HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
05/24/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/533,084	VAUTHIER ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 14 May 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires *5* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☐ Applicant's reply has overcome the following rejection(s): _____.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-2, 5-6, 8-10, 15-16 and 19-20, and new claims 24-30 would be rejected*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☒ Other: See Continuation Sheet.

/Anne Marie S. Wehbe/
Primary Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because: Pages 7-15 of Applicant's Arguments/Remarks Made in Amendment provide arguments that are duplicated from the Applicant's Arguments/Remarks Made in Amendment filed September 8, 2009. Such were considered and addressed in the prior Office Action, and will not be iterated herein. The Examiner will address Applicant's new argument(s) pertaining to the instant rejection.

Applicant argues that Kabanov does not specifically disclose hemoproteins nor hemoglobin.
Applicant's argument(s) has been fully considered, but is not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, Schmidt et al disclosed the biolgcal agent is a hemoprotein or hemoglobin.

Applicant argues that the nanogels of the cited art [Kabanov] are porous materials and the immobilization of the biological agents (such as proteins) in the nanogel networks is in the entire volume of the network rather than on the surface.
Applicant's argument(s) has been fully considered, but is not persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., immobilization of the biological aent on the surface) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).
Chauvierre discloses the nanoparticle structure of the instant claims of which the polysaccharide forms the shell. Kabanov et al disclosed the polymer network can also be loaded non-covalently with the biological agent after the network is synthesized (col. 13, lines 1-22; Examples 7-9), wherein the polymer network captures the biological agent that may be a protein. Thus, to the extent that the polysaccharide network is on the surface of the nanoparticle, it is axiomatic that the hemoglobin [Schmidt] will also be present on the nanoparticle surface.

Applicant argues that, upon consideration of [Gray, 2004; Belezza, 2007; Iafisco, 2008; and Henzler, 2007] which support the fact that it could not be reasonably predicted that noncovalent association of a hemoprotein on the surface of the claimed nanoparticles would not result in loss of functionality of the hemoprotein. The references, published after the present application was filed, demonstrate that the claimed invention was not predictable from the cited art.
Applicant's argument(s) has been fully considered, but is not persuasive. Gray, 2004; Belezza, 2007; Iafisco, 2008; and Henzler, 2007 are post-filing art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP §2164.05(a)) Thus, in effect, Applicant is using information published five years after the priority date of the instant invention to exercise improper hindsight and improperly argue the unpredictability in the art at the time [emphasis added] of the invention.

Furthermore, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., immobilization of the biological aent on the surface) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the claims place no minimal amount of hemoglobin functional activity, and thus any amount of activity is sufficient.
With respect to Gray, while a [unspecificied] protein may experience unfolding when adsorbed onton a [unspecified] solid surface, protein adsorption behavior is dependent on the individual nature of the protein and the surface involved. Notwithstanding the lack of understanding regarding the specific structural details of a [unspecified] protein when it adsorbs to a [unspecified] surface and/or the corresponding thermodynamics, the adsorption of proteins onto nanoparticles was routinely practiced in the art (Gray; pg 110, col. 2; pg 112, col. 1).
With respect to Belezza, the Examiner notes that myoglobin retained significant activity when adsorbed to the nanoparticles (Figure 2), and thus the post-filing art demonstrates that the adsorption of hemoproteins onto a surface does not result in the absolute loss of functionality of the hemoprotein.
With respect to Iafisco, the authors do not speak to the functionality of the hemoprotein. While some myoglobin proteins may undergo conformational change, there is no evidence for loss of functionality.
WIth respect to Henzler, the authors do not measure the functionality of the hemoprotein. While some activity may be lost, at least some activity may be retained.

Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). The teachings of Chauvierre, Kabanov, Schmidt and Desai establish that those of ordinary skill in the art would have possessed a reasonable expectation of success for nanoparticles comprising hemoprotein adsorbed onto a surface to retain hemoprotein activity because Kabanov et al successfully demonstrated the ability to non-covalently associate a biological agent, e.g. a therapeutic protein, to a nanoparticle comprising a nanogel network, wherein said nanogel network may comprise heparin, Schmidt et al successfully demonstrated the manufacture of polysaccharide-hemoglobin conjugates for the formation of a blood substitute in which the hemoglobin is attached non-covalently to the polysaccharide, and Applicant's own work teaches that prior to the instantly asserted invention, those of ordinary skill in the art had long recognized that heparin, being polyanionic in nature, has a high affinity for basic proteins like hemoglobin (Haney et al, 2000; reference 19 of Chauvierre et al, 2004a; * of record), and thus those of ordinary skill in the art would immediately recognize a reasonable expectation of success for the formation of a non-covalent association between hemoglobin and heparin. An artisan would have been motivated to modify the heparin-coated poly(cyanoacrylate) nanoparticle of Chauvierre et al to comprise

hemoglobin conjugated non-covalently as per Kabanov et al and Schmidt et al for the formation of a blood substitute product because the heparin moiety, well known in the art to act as an anti-coagulant as well as to inhibit complement activation, already tailors the nanoparticle for increased circulating half-life of the nanoparticle, and thus would provide an artisan with the desired delivery vehicle for a blood substitute, and Schmidt et al disclose that all of the hemoglobin-containing molecules comprising a covalent bond between the cross-linking agent or polymer results in a change in the hemoglobin structure, thereby adversely affecting oxygen transport, impairing oxygen release, reduced hemoglobin cooperativity, and an undesired increase in oxygen affinity disadvantageous for use as a blood substitute (col. 2, lines 16-53). The non-covalent association of hemoglobin with the polysaccharide-ligand overcomes the art-recognized disadvantageous properties.

Applicant argues that the ordinary artisan would expect the nanoparticles to activate the complement system (per the teachings of Andersson et al (2005).
Applicant's argument has been fully considered, but is unpersuasive. Andersson is post-filing art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP §2164.05(a)). It is unclear how Applicant can reasonably expect the ordinary artisan to use information published at least three years in the future [after the priority date of the instant application] to affect the artisan's knowledge and actions in the present. Rather, in effect, Applicant is exercising improper hindsight to argue any unpredictability in the art at the time [emphasis added] of the invention.

Applicant argues that the present invention unexpectedly provides nanoparticles whose physicochemical properties are not substantially altered upon non-covalent association with hemoglobin. One of the important physico-chemical properties is the hydrodynamic radius of the nanoparticles, which the inventors have discovered to not be significantly altered by non-covalent association of hemoglobin..
Applicant's argument has been fully considered, but is unpersuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., hydrodynamic radius of the nanoparticles) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant argues that the process by which the instantly claimed hemoglobin-non-covalently-associated nanoparticles are prepared yields much lower cytotoxicity than the hemoglobin-non-covalently-associated nanoparticles of the prior art.
Applicant's argument has been fully considered, but is unpersuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., redox radical emultion polymerization process steps) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Continuation of 13. Other: New Claims 24-30, substantial duplicates of Claims 1, 5-6, 8, 10 and 15-16, would be rejected for reasons of record, as the prior art teaches the hemoprotein to be hemoglobin..